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08/945425

F. .ENT COOPERATION TREA.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 February 1998 (06.02.98)	
International application No. PCT/SE97/01098	**Applicant's or agent's file reference** H 1583-1 WO
International filing date (day/month/year) 18 June 1997 (18.06.97)	**Priority date** (day/month/year) 20 June 1996 (20.06.96)
Applicant CEDERBERG, Christer et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 January 1998 (15.01.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

3630

08/945425

19

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

26 OCT 1998

WIPO PCT

Applicant's or agent's file reference H 1583-1 WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE97/01098	International filing date *(day/month/year)* 18.06.1997	Priority date *(day/month/year)* 20.06.1996
International Patent Classification (IPC) or national classification and IPC6 A 61 K 9/00, A 61 K 31/44		
Applicant Astra AB (publ) et al		

FEB 12 1999

GROUP 1800

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.01.1998	19.10.1998
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Anneli Jönsson Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE97/01098

I Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☐ the international application as originally filed.

☒ the description, pages 1-11 , as originally filed,
pages _____ , filed with the demand,
pages _____ , filed with the letter of _____ ,
pages _____ , filed with the letter of _____ .

☒ the claims, Nos. _____ , as originally filed,
Nos. _____ , as amended under Article 19,
Nos. _____ , filed with the demand,
Nos. 1-17 , filed with the letter of 11.09.1998 ,
Nos. _____ , filed with the letter of _____ .

☒ the drawings, ~~sheets~~/fig 1 , as originally filed,
~~sheets~~/fig _____ , filed with the demand
~~sheets~~/fig _____ , filed with the letter of _____ ,
~~sheets~~/fig _____ , filed with the letter of _____ .

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE97/01098

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-6*, 15-17

because:

☒ the said international application, or the said claims Nos. 1-6*, 15-17
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1 (iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

* Claims 1-6 are considered to cover the same scope as claims 15-17 as a "regimen" is considered to be a method for treatment

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been establised for said claims Nos. _____

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE97/01098

V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	7-14	YES
	Claims		NO
Inventive step (IS)	Claims	7-14	YES
	Claims		NO
Industrial applicability (IA)	Claims	7-14	YES
	Claims		NO

2. Citations and explanations

The claimed invention relates to an oral pharmaceutical composition giving an extended blood plasma profile of a H^+,K^+-ATPase inhibitor, such as omeprazole. An improved gastric secretion is obtained by an extended blood plasma profile of the H+,K+-ATPase inhibitor. Also the use of the oral pharmaceutical composition is claimed. A more effective utilisation of the total amount of the drug is obtained by a repeated dosing of an extended release formulation, despite the long duration of the pharmacological effect by the H^+, K^+-ATPase inhibitor.

Documents WO 9601623 A1 and US 4 853 230 A disclose different dosage forms comprising omeprazole, a multiple unit tableted dosage form and enteric coated tablets or capsules respectively. The uses of the preparations are described. The dosage forms are administered one to several times a day and the dose will depend on the individual requirements of the patients, mode of administration and the disease. The drug is not administered by an extended release. The documents do not give the information that a dose divided in two consecutively administered doses will result in a different inhibition of the proton pump than the drug in one single dose. The documents only discloses the general state of the prior art.

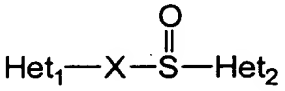
From John E Hoover "Remingtons Pharmaceutical Sciences", fifteenth edition, 1975, Mack Publishing Company, page 702, col 1, line 43-col 2, line 6, it is known to calculate a dosage regimen from kinetics of absorption, distribution and elimination of a single dose. By these calculations a optimal plasma concentration or body content may be determined. The document only disclose the general state of the prior art.

Consequently, the claimed invention according to claims 7-14 is considered to involve novelty, inventive step and industrial applicability.

PCT/SE97/01093
11 -09- 1998

Amended claims

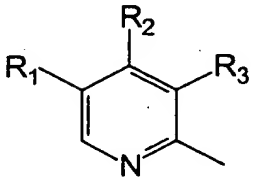
1. An administration regimen for improved inhibition of gastric acid secretion characterized in that an extended blood plasma profile of a H^+, K^+-ATPase inhibitor is obtained and that said H^+, K^+-ATPase inhibitor is a compound with the formula I



I

wherein

Het_1 is



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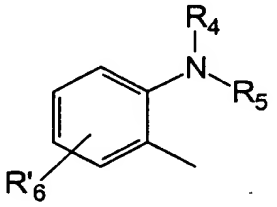

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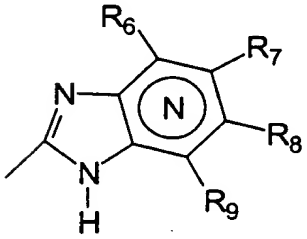

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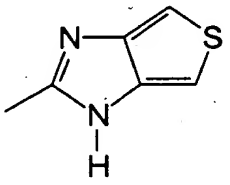

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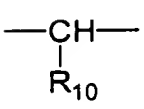

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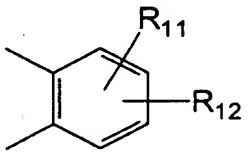


and wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;
R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl.

2. An administration regimen according to claim 1 characterized in that the H^+, K^+-ATPase inhibitor is a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole.

3. An administration regimen giving an extended blood plasma profile of a H^+, K^+-ATPase inhibitor according to any of claims1 and 2 characterized in that the extended plasma profile is obtained by two or more consecutive oral administrations of a unit dose of the H^+, K^+-ATPase inhibitor with 0.5 - 4 hours intervals.

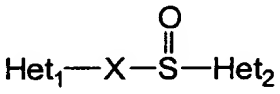
4. An administration regimen giving an extended blood plasma profile of a H^+, K^+-ATPase inhibitor according to claim 1 characterized in that the extended plasma profile is obtained by oral administration of a unit dose of a pharmaceutical

preparation which releases the drug for absorption in two or more discrete pulses separated in time by 0.5 - 4 hours.

5. An administration regimen according to claim 1, characterized in that the extended plasma profile is obtained by oral administration of a unit dose of a pharmaceutical preparation which releases the H^+, K^+-ATPase inhibitor for absorption with an almost constant rate during an extended time period.

6. An administration regimen according to any of claims 1 - 5 characterized in that the extended plasma profile is received during 2 - 12 hours.

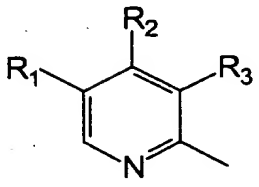
7. An oral pharmaceutical composition giving an extended blood plasma profile of a H^+, K^+-ATPase inhibitor, characterized in that the H^+, K^+-ATPase inhibitor is a compound with the formula I



I

wherein

Het_1 is



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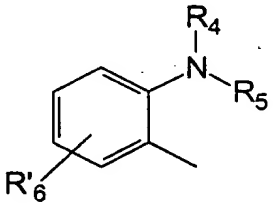

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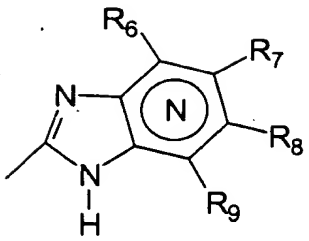

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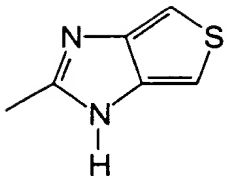

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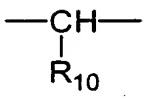

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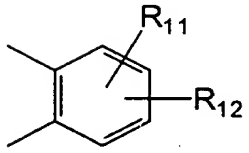

wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;
R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl.

8. An oral pharmaceutical preparation according to claim 7, characterized in that the H^+, K^+-ATPase inhibitor is a compound selected from the group of omeprazole, an

alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole.

9. An oral pharmaceutical preparation giving an extended blood plasma profile of a H^+, K^+-ATPase inhibitor according to claim 7 characterized in that the pharmaceutical preparation releases the drug for absorption in two or more discrete pulses separated in time by 0.5 - 4 hours.

10. An oral pharmaceutical preparation according to claim 7, characterized in that the pharmaceutical preparation releases the H^+, K^+-ATPase inhibitor for absorption with an almost constant rate during an extended time period.

11. An oral pharmaceutical preparation giving an extended blood plasma profile of a H^+, K^+-ATPase inhibitor according to any of claims 7 - 10 characterized in that the extended plasma profile is received during 2 -12 hours.

12. Use of an oral pharmaceutical composition as claimed in any of claims 7 - 10 in the manufacture of a medicament with improved inhibition of gastric acid secretion.

13. Use of an oral pharmaceutical composition as claimed in any of claims 7 - 10 in the manufacture of a medicament with improved therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion.

14. Use of H^+, K^+ - ATPase inhibitor with the formula I defined in claim 1, for the preparation of a pharmaceutical composition with extended release.

15. A method for improving inhibition of gastric acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical composition as claimed in any of claims 7 - 10.

16. A method for improving the therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion which comprises

administering to a patient in need thereof, an oral pharmaceutical composition as claimed in any claims 7 - 10.

17. A method for receiving an extended plasma profile of a H^+, K^+- ATPase inhibitor by administering to a patient in need thereof a pharmaceutical preparation with extended release of a H^+, K^+- ATPase inhibitor as defined in claim 1.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) H 1583-1 WO

Box No. I TITLE OF INVENTION

ADMINISTRATION OF PHARMACEUTICALS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

ASTRA AKTIEBOLAG
S-151 85 SÖDERTÄLJE
Sweden

☐ This person is also inventor.

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.
19237 ASTRA S

State *(i.e. country)* of nationality: SE

State *(i.e. country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

CEDERBERG, Christer
Åkergatan 1
S-431 69 Mölndal
Sweden

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: SE

State *(i.e. country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Patent Department
Astra Aktiebolag
S-151 85 SÖDERTÄLJE
Sweden

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.
19237 ASTRA S

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

SACHS, George
17986 Boris Drive
Encino, CA 91316
USA

This person is:

- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of:

- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of:

- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of:

- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of:

- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ **AP** **ARIPO Patent:** KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ **AL** Albania
- ☒ **AM** Armenia
- ☒ **AT** Austria
- ☒ **AU** Australia
- ☒ **AZ** Azerbaijan
- ☒ **BA** Bosnia and Herzegovina
- ☒ **BB** Barbados
- ☒ **BG** Bulgaria
- ☒ **BR** Brazil
- ☒ **BY** Belarus
- ☒ **CA** Canada
- ☒ **CH and LI** Switzerland and Liechtenstein
- ☒ **CN** China
- ☒ **CU** Cuba
- ☒ **CZ** Czech Republic
- ☒ **DE** Germany
- ☒ **DK** Denmark
- ☒ **EE** Estonia
- ☒ **ES** Spain
- ☒ **FI** Finland
- ☒ **GB** United Kingdom
- ☒ **GE** Georgia
- ☒ **HU** Hungary
- ☒ **IL** Israel
- ☒ **IS** Iceland
- ☒ **JP** Japan
- ☒ **KE** Kenya
- ☒ **KG** Kyrgyzstan
- ☒ **KP** Democratic People's Republic of Korea
- ☒ **KR** Republic of Korea
- ☒ **KZ** Kazakstan
- ☒ **LC** Saint Lucia
- ☒ **LK** Sri Lanka
- ☒ **LR** Liberia
- ☒ **LS** Lesotho
- ☒ **LT** Lithuania
- ☒ **LU** Luxembourg
- ☒ **LV** Latvia
- ☒ **MD** Republic of Moldova
- ☒ **MG** Madagascar
- ☒ **MK** The former Yugoslav Republic of Macedonia
- ☒ **MN** Mongolia
- ☒ **MW** Malawi
- ☒ **MX** Mexico
- ☒ **NO** Norway
- ☒ **NZ** New Zealand
- ☒ **PL** Poland
- ☒ **PT** Portugal
- ☒ **RO** Romania
- ☒ **RU** Russian Federation
- ☒ **SD** Sudan
- ☒ **SE** Sweden
- ☒ **SG** Singapore
- ☒ **SI** Slovenia
- ☒ **SK** Slovakia
- ☒ **TJ** Tajikistan
- ☒ **TM** Turkmenistan
- ☒ **TR** Turkey
- ☒ **TT** Trinidad and Tobago
- ☒ **UA** Ukraine
- ☒ **UG** Uganda
- ☒ **US** United States of America
- ☒ **UZ** Uzbekistan
- ☒ **VN** Viet Nam

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☒ YU Yugoslavia
- ☒ GH Ghana
- ☒ ZW Zimbabwe
- ☒ SL Sierra Leone

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____.

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1) SE	20 June 1996 (20.06.1996)	9602442-7	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) : (1)

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA / SE

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:*

Country (or regional Office):	Date *(day/month/year)*:	Number:
SE	20 June 1996	9602442-7

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	:	4 sheets
2. description	:	11 sheets
3. claims	:	6 sheets
4. abstract	:	1 sheets
5. drawings	:	1 sheets
Total	:	23 sheets

This international application is accompanied by the item(s) marked below:

1. ☒ separate signed power of attorney
2. ☒ copy of general power of attorney GF 1583/96 & GF 99/97
3. ☐ statement explaining lack of signature
4. ☐ priority document(s) *identified in Box No. VI as item(s):*
5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☒ other *(specify)*: ITS 9602442-7

Figure No. 1 of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Södertälje, 18 June 1997

Birgitta Larsson

Birgitta Larsson, Patent Department, Astra Aktiebolag

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority specified by the applicant: ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

INTERNATIONAL SEARCH REPORT

Internati nal application No.
PCT/SE 95/00678

Box I Observations where certain claims were f und unsearchable (Continuation f item 1 of first sheet)

This international search report has not been established in respect of certain claims under Articl 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19-20
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark n Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] N protest accompanied the payment of additi nal search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 95/00678

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0247983	02/12/87	SE-T3- 0247983	
		AU-B- 601974	27/09/90
		AU-A- 7191287	05/11/87
		CA-A- 1292693	03/12/91
		DE-A- 3783394	18/02/93
		DK-B- 169988	24/04/95
		EP-A,A,A 0496437	29/07/92
		EP-A,A- 0567201	27/10/93
		ES-T- 2006457	01/01/94
		GB-A- 2189698	04/11/87
		HK-A- 135294	09/12/94
		IE-B- 61416	02/11/94
		JP-C- 1863556	08/08/94
		JP-A- 5294831	09/11/93
		JP-A- 62258320	10/11/87
		NO-B,C- 174239	27/12/93
		SU-A- 1820837	07/06/93
		US-A- 4786505	22/11/88
EP-A1- 0519144	23/12/92	NONE	
EP-A1- 0365947	02/05/90	SE-T3- 0365947	
		AU-B- 612525	11/07/91
		AU-A- 4365089	03/05/90
		CA-A- 2000932	26/04/90
		DE-T- 68907177	13/01/94
		ES-T- 2055775	01/09/94
		HK-A- 123394	18/11/94
		JP-A- 2164821	25/06/90
		SE-A- 8803822	26/10/88
		US-A- 5178868	12/01/93
WO-A1- 9222284	23/12/92	AU-A- 1974692	12/01/93
		BG-A- 98286	15/08/94
		CN-A- 1067809	13/01/93
		CZ-A- 9302764	13/07/94
		DE-A- 4219390	24/12/92
		EP-A- 0519365	23/12/92
		EP-A- 0589981	06/04/94
		FI-D- 935677	00/00/00
		JP-T- 6508118	14/09/94
		NO-A,D- 934648	16/12/93

#2

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference H 1583-1 WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE97/01098	International filing date (day/month/year) 18.06.1997	Priority date (day/month/year) 20.06.1996
International Patent Classification (IPC) or national classification and IPC A 61 K 9/00, A 61 K 31/44		
Applicant Astra AB (publ) et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.01.1998	19.10.1998
Name and mailing address of the IPEA/SE [illegible] Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Authorized officer Anneli Jönsson Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE97/01098

I Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☐ the international application as originally filed.

☒ the description, pages 1-11, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____.
pages _____, filed with the letter of _____

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-17, filed with the letter of 11.09.1998.
Nos. _____, filed with the letter of _____

☒ the drawings, ~~sheets~~/fig 1, as originally filed,
~~sheets~~/fig _____, filed with the demand
~~sheets~~/fig _____, filed with the letter of _____.
~~sheets~~/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE97/01098

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-6*, 15 17

because:

☒ the said international application, or the said claims Nos. 1 6*, 15 17 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1 (iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

* Claims 1-6 are considered to cover the same scope as claims 15-17 as a "regimen" is considered to be a method for treatment

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been establised for said claims Nos _____

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE97/01098

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	7-14	YES
	Claims		NO
Inventive step (IS)	Claims	7-14	YES
	Claims		NO
Industrial applicability (IA)	Claims	7-14	YES
	Claims		NO

2. Citations and explanations

The claimed invention relates to an oral pharmaceutical composition giving an extended blood plasma profile of a H^+,K^+-ATPase inhibitor, such as omeprazole. An improved gastric secretion is obtained by an extended blood plasma profile of the H+,K+-ATPase inhibitor. Also the use of the oral pharmaceutical composition is claimed. A more effective utilisation of the total amount of the drug is obtained by a repeated dosing of an extended release formulation, despite the long duration of the pharmacological effect by the H^+, K^+-ATPase inhibitor.

Documents WO 9601623 A1 and US 4 853 230 A disclose different dosage forms comprising omeprazole, a multiple unit tableted dosage form and enteric coated tablets or capsules respectively. The uses of the preparations are described. The dosage forms are administered one to several times a day and the dose will depend on the individual requirements of the patients, mode of administration and the disease. The drug is not administered by an extended release. The documents do not give the information that a dose divided in two consecutively administered doses will result in a different inhibition of the proton pump than the drug in one single dose. The documents only discloses the general state of the prior art.

From John E Hoover "Remingtons Pharmaceutical Sciences", fifteenth edition, 1975, Mack Publishing Company, page 702, col 1, line 43-col 2, line 6, it is known to calculate a dosage regimen from kinetics of absorption, distribution and elimination of a single dose. By these calculations a optimal plasma concentration or body content may be determined. The document only disclose the general state of the prior art.

Consequently, the claimed invention according to claims 7-14 is considered to involve novelty, inventive step and industrial applicability.